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Note

Syntheses of 1,5-benzothiazepines: Part XVIII-Syntheses of potential, fluorinated 2,4-diaryl-8-ethoxy / fluoro-2,5-dihydro-1,5-benzothiazepines as prospective cardiovascular agents

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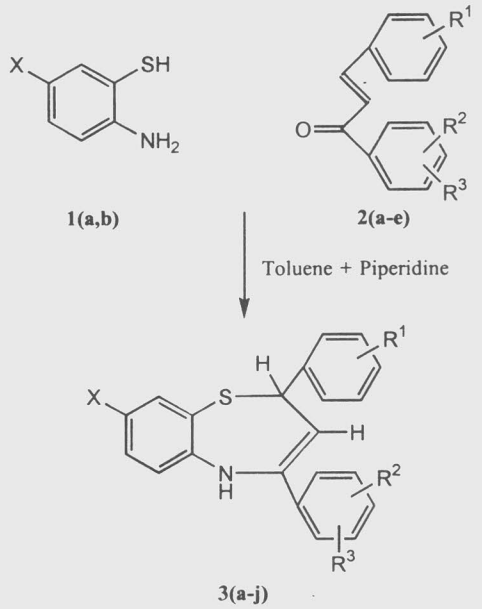
5-Ethoxy- and 5-fluoro-2-aminobenzenethiols have been reacted with fluorinated benzalacetophenones **2a-e** to obtain respective 2,4-fluorinated diaryl-8-ethoxy/fluoro-2,5-dihydro-1,5-benzothiazepines **3a-j** in satisfactory yields (40 - 58%). These compounds have been characterized by elemental analyses for nitrogen and IR, ^{1}H NMR, ^{19}F NMR and mass spectral studies.

A number of fluorinated 1,4-and 1,5-benzodiazepine class of compounds have been introduced as psychopharmacological and cardiovascular agents such as fluorodiazepam[1], used as a CNS stimulant, tifluadam[2], a cholecystokinin antagonist and analgesic, flurazepam[3] and flunitrazepam[4], hypnotic, fletazepam[5], a skeletal muscle relaxant and triflubazam[6], a cardiovascular agent, anticonvulsant and CNS depressant. Looking to the importance of fluorinated heterocycles and in continuation of our work[7] on the syntheses of analogous fluorinated 8-substituted-1,5-benzothiazepines as possible potentially bioactive compounds, we report herein the syntheses of ten new fluorinated compounds, 2,4-diaryl-8-fluoro / ethoxy-2, 5-dihydro-1,5-benzo-thiazepines. 5-Ethoxy and 5-fluoro-2-amino-benzene-thiols **(1a** and **1b)** were reacted with five fluorinated



Compd	R^1	R^2	R^3	X
3a	4–F	H	H	F
b	4–F	H	H	OC_2H_5
c	H	4–F	H	F
d	H	4–F	H	OC_2H_5
e	4–F	4–F	H	H
f	4–F	4–F	H	OC_2H_5
g	4–F	4–F	3–Cl	F
h	4–F	4–F	3–Cl	OC_2H_5
i	4–F	4–F	2–CH_3	F
j	4–F	4–F	2–CH_3	OC_2H_5

chalcones, 4-fluorobenzalacetophenone **2a,** benzal-4'-fluoroacetophenone **2b,** 4-fluoro-benzal-4'-fluoroacetophenone **2c,** 4-fluorobenzal-3'-chloro-4'-fluoroacetophenone **2d** and 4-fluoro-benzal-4'-fluoro-2'-methylacetophenone **2e.** The chalcones, **2a-c** were prepared by literature methods[8,9] and **2d** and **2e** were also prepared by similar procedure, their structures being confirmed by making a comparative study. The IR spectra of these were found to exhibit, the strong carbonyl peak absorbing in the range 1680-1665 cm^{-1}. The ^{1}H NMR spectra showed signals for their olifinic protons alongwith aromatic protons in the

Table I— Physical characterization data and elemental analysis of 2,4-diaryl-2,5-dihydro-8-ethoxy/fluoro-1,5-benzothiazepines **3 a-i**

Compd	X	R^1	R^2, R^3	Period (hr)	m.p. (°C)	R_f	Yield (%)	Mol. formula (Mol. wt)	Nitrogen (%) Found (Calcd)
3a	F	4-F	H	8	80	0.89	46	$C_{21}H_{15}NSF_2$ (351)	4.01 (3.98)
b	OC_2H_5	4-F	H	6	95	0.91	55	$C_{23}H_{20}NSOF$ (377)	3.75 (3.71)
c	F	H	4-F	7	82	0.84	45	$C_{21}H_{15}NSF_2$ (351)	4.00 (3.98)
d	OC_2H_5	H	4-F	6	99	0.89	58	$C_{23}H_{20}NSOF$ (377)	3.74 (3.71)
e	F	4-F	4-F	18	180	0.76	41	$C_{21}H_{14}NSF_3$ (369)	3.82 (3.79)
f	OC_2H_5	4-F	4-F	15	240	0.78	49	$C_{23}H_{19}NSOF_2$ (395)	3.55 (3.52)
g	F	4-F	3-Cl,4-F	12	120	0.77	40	$C_{21}H_{13}NSF_3Cl$ (403.5)	3.50 (3.47)
h	OC_2H_5	4-F	3-Cl,4-F	10	150	0.84	43	$C_{23}H_{18}NSOF_3Cl$ (448.5)	3.15 (3.12)
i	F	4-F	2-CH_3,4-F	11	78	0.74	54	$C_{22}H_{16}NSF_3$ (383)	3.69 (3.64)

downfield region at δ 6.4-8.3. Further, in ^{19}F NMR, the number of fluorine atoms in each compound were detected by the same number of signals in the range, -103.9 to -114.79 ppm.

Observed as earlier[10-12], the reaction between chalcones **2a-e** and 5-substituted-2-aminobenzenethiols **1a,b** afforded the final products in one step. The reactions were carried out in dry toluene basified with piperidine (10:1) and the progress of the reaction being monitored by TLC.

In the IR spectra of the products **3a-j,** characteristic absorption bands in the range 1680-1665 cm^{-1} due to carbonyl group of chalcone and two bands around 3450 cm^{-1} and 3350 cm^{-1} due to primary amino group were found to be absent. These observations indicated that the reaction between **1a,b** and **2a-e** had taken place to give the final products. The physical characterization data of compounds **3a-i** are given in Table I. A broad absorption band appearing in the region 3210-3140 cm^{-1} is assigned to the presence of a hydrogen bonded secondary amino group (Table II).

In ^1H NMR spectra the downfield absorption at δ 6.6-7.0 (1H, d, *J*=8-9 Hz, C-2-H), 6.8-7.2 (1H, d, *J*=8-9 Hz, C-3-H) may be assigned due to C-2-H being attached with electronegative sulphur and being in the deshielding zone of aryl group and C-3-H being vinyl. Multiplets observed in the region δ 6.5-8.3 are assigned to the aromatic protons (Table II). The spectra of **3b, d, f, h, j** showed a triplet around δ 1.25-1.40 (*J*=7Hz, 3H) and a quartet around δ 3.74-4.20 (*J*=7Hz, 2H) due to ethoxyl group. The spectra of **3i, j** absorbed at δ 1.55-1.57 (3H, s) which may be assigned to methyl protons. All the spectra showed absorption at around δ 3.0-3.6 (1H, b, N-H) suggesting an enamine structure[12].

^{19}F NMR spectra gave singlet signals in the range −130.84 to −114.92 ppm corresponding to number of fluorine atoms (Table II). The (m/z) $[M]^+$ peaks corresponded to the calculated values of molecular weights of the compounds.

Experimental Section

The recorded melting points are uncorrected. TLC using benzene : methanol : ammonia (8:1:1)

Table II - IR, ^{1}H NMR and ^{19}F NMR spectral data of 2,4-diaryl-2,5-dihydro-8-ethoxy/fluoro-1,5-benzothiazepines **3 a-i**

Compd	IR (cm^{-1}) ν (N-H)	^{1}H NMR, δ values, J in Hz				^{19}F NMR, values in ppm
		C-2-H	C-3-H	OCH_2CH_3/CH_3	Ar-H	C-8-F/C-4'-F/C-4"-F
3a	3210-3195	6.68 (d,1H, J=9)	6.9 (d,1H, J=9)	-	6.6-7.68 (m,12H)	-107.69,-114.92
b	3220-3150	6.6 (d,1H, J=8)	6.76 (d,1H, J=8)	1.25 (t, J=7,3H), 3.74 (q, J=7,2H)	6.5-7.45 (m,.12H)	-114.84
c	3220-3170	6.67 (d,1H, J=9)	6.88 (d,1H, J=9)	-	6.6-7.65 (m,12H)	-107.55,-103.84
d	3215-3165	6.62 (d,1H, J=8)	6.81 (d,1H, J=8)	1.34 (t, J=7,3H), 3.8 (q, J=7,2H,)	6.5-7.4 (m,.12H)	-103.96
e	3220-3140	6.92 (d,1H, J=9)	7.13 (d,1H, J=9)	-	7.15-8.3 (m,11H)	-107.24,-107.96,-104.44
f	3225-3140	6.98 (d,1H, J=9)	7.19 (d,1H, J=9)	1.27 (t, J=7,3H) 3.76 (q, J=7,2H)	7.0-8.15 (m,11H)	-107.72,-104.31
g	3205-3140	6.96 (d,1H, J=9)	7.18 (d,1H, J=9)	-	6.8-8.25 (m,10H)	-107.57,-107.33,-113.69
h	3200-3150	6.98 (d,1H, J=9)	7.2 (d,1H, J=9)	1.49 (t, J=7,3H), 4.2 (q, J=7,2H)	6.9-8.3 (m,.10H)	-107.7,-113.62
i	3210-3180	6.88 (d,1H, J=8)	7.05 (d,1H, J=8)	1.55 (s,3H)	6.8-7.7 (m,10H)	-107.78,-107.54,-108.25

as irrigant was used for monitoring progress of reaction and for checking purity of the compounds. IR spectra were recorded in KBr pellets on Magna FT IR -550 spectrometer, mass spectra on Jeol D-300 (EI/CI) instrument at 70 ev and ^{1}H NMR and ^{19}F NMR spectra were taken on a Jeol machine (model FX 90Q) using $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR at 89.55 MHz and hexafluorobenzene as external standard for ^{19}F NMR at 84.25 MHz. 5-Ethoxy- and 5-fluoro-2-aminobenzenethiols were prepared from literature methods[13].

4-Fluoroacetophenone[14], 3-chloro-4-fluoro-aceto-phenone[14] and 4-fluoro-2-methylaceto-phenone[15] were prepared from fluorobenzene, *o*-chlorofluoro-benzene and *m*-fluorotoluene respectively by the application of Frieded-Crafts reaction.

The chalcones, 4-fluorobenzalacetophenone (84°C, **2a**), benzal-4'-fluoroacetophenone (80°C, **2b**) and 4-fluorobenzal-4'-fluoroacetophenone (104°C, **2c**) were prepared by literature methods[8,9] by stirring equimolar quantities of respective aromatic aldehydes and acetophenones in ethanol in the presence of 50% NaOH at room temperature (25°C) till light coloured crude solids were obtained which were crystallized from ethanol. Preparation of 4-fluorobenzal-3'-chloro-4'-fluoroacetophenone (**2d,** m.p.90°C, yield 62%) requires stirring for 10 hr at 60°C whereas 4-fluorobenzal-4'-fluoro-2'-methylacetophenone (**2e,** m.p. 75°C, yield 70%) was obtained within 20 min.

8-Ethoxy-2-(4- fluorophenyl)-4-(4-fluoro-2-methylphenyl)-2, 5-dihydro-1,5-benzothiaze-pines 3j. A mixture of 2-amino-5- ethoxybenzen-ethiol (**1b,** 0.17 g, 0.001 mole) and 4-fluorobenzal-4'- fluoro-2-methylbenzalacetophenone (**2e,** 0.26 g, 0.001 mole) in toluene (10 mL) containing piperidine (1 mL) was stirred and refluxed for 8 hr. On completion of the reaction, as monitored by TLC and final colour change from yellow to dark red, toluene was removed under reduced pressure. The crude product was washed repeatedly with small amounts of pet. ether (60-80°) and

crystallized from a combination of benzene and methanol (80:20) to obtain dark green shining crystals of **3j**, m.p. 134°C, yield 0.21 g (51%). IR : 3210 cm^{-1} (N-H); ^1H NMR : δ 1.40 [(3H, t, *J*=7Hz, 8-O-CH_2CH_3, δ 4.08 (2H, q, *J*=7Hz, 8-OCH_2CH_3)], δ 1.57 (3H, s, CH_3), 3.25 (1H, b, NH), δ 6.9 (1H, d, C-2-H, *J*=8Hz), 7.08 (1H, d, C-3-H, *J*=8Hz), δ 7.15-8.25 (12H, m, ArH); ^{19}F NMR : -108.77 ppm (s, 1F, C-4"-F or C-4'-F), -108.69 ppm (s, 1F, C-4'-F or C-4"-F) (Found : N, 3.45. $C_{24}H_{21}NSOF_2$ requires N, 3.42%); MS : Found : m/z 409 $[M]^+$. Calcd : 409.

Following the same procedure by reflux heating or variable time period compounds **3a-j** were obtained (Table I). Characteristic absorption peaks in IR, ^1H NMR and ^{19}F NMR spectra are given in Table II.

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